Orotic Acid

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Contents

Preface

This volume reviews a series of different publications dealing with orotic acid. Orotic acid was isolated from cow's milk 75 years ago by Biscaro and Belloni in Italy. Fifty years later again Italian scientists described the growth-promoting activity of orotic acid in vitamin B_{12}-deficient animals. Orotic acid is the precursor of pyrimidine nucleotides which are involved in many biochemical reactions: UTP and CTP, as substrates for RNA polymerase, and UDP sugars, as substrates for carbohydrate containing macromolecules, e.g. glycogen, glycoproteins and glycolipids. The biosynthesis of these pyrimidines is well regulated. Disturbance of the biosynthetic pathway or trapping of individual pyrimidine nucleotides may lead to severe metabolic and structural alterations of cells. Synthesis, biochemical aspects and physiological role are reviewed in nine chapters. In the last two decades increasing interest in orotic acid came from several studies showing protective or therapeutic or beneficial effects of this compound in different kinds of organ injuries: various forms of hepatic insufficiency, myocardial infarction, encephalopathy, memorization processes, mentioned in Chapters 8 and 9.

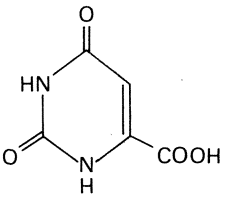
At the end of this overview a Bibliography in an alphabetical order with 673 references may give further insight in this topic.

A. Čihák
W. Reutter

Orotic Acid: Synthesis, Biochemical Aspects and Physiological Role

1. New Growth Factor?

Orotic acid was isolated by Biscaro and Belloni [1] in Italy in 1905 from cow's milk where it constitutes the major pyrimidine. While cow's milk and commercial powdered milk [2] have a relatively high content of orotic acid (50–100 mg l^{-1} and 100–130 mg per 100 g protein respectively) human milk contains only trace amounts of orotic acid [3,4]. Its concentration in other foods is not yet known. There are several reports dealing with the amount of orotic acid in milk and milk products (chocolate, food milk powders etc.) [5–12] and several different techniques were developed for the measurement of its concentration [13–16].



Orotic acid

In addition to its importance in the synthesis of nucleic acids and other substances containing pyrimidine, evidence began to accumulate indicating that this 2,6-dioxypyrimidine derivative might be one of the growth factors in animals [17–19]. The physiological role of orotic acid [20–23] was first studied mainly in Italy, Sweden and the United States and later in Germany, Hungary and the Soviet Union (Chapters 8 and 9).

Italian scientists focussed their attention on the growth-promoting action of orotic acid in vitamin B_{12}-deficient rats and chicks [24, 25]. Orotic acid and vitamin B_{12} have similar effects on the metabolism of the C_1-unit, whereby orotic acid increases the concentration of folate derivatives and influences the enzymes involved in the synthesis and utilization of folate intermediates [26,27]. Orotic acid also results in an increase in liver RNA concomitant with the stimulation of nuclear DNA-dependent RNA polymerase activity [28,29]. These findings led to the presumption that orotic acid increases messenger RNA synthesis. There are a number of further reports, mainly from Italy [30–47], dealing with the relationship between orotic acid and vitamin deficiency, distribution and function [48–61].

Orotic acid is used at present as a therapeutic agent in neonatal jaundice, myocardial infarction, and various forms of hepatic insufficiency (Chapter 9). Therapeutic effects of orotic acid have been investigated in a number of conditions, usually with beneficial results, since its administration results in a higher level of pyrimidine precursors of nucleic acids and also the

pyrimidine cofactors essential for the conversion of carbohydrates, lipids and some other metabolites. This leads to an increase in the rate and capacity of different metabolic pathways where pyrimidine components are operating, and to the promotion of the growth of the organism [62,63].

In this review several aspects relating to the biochemical and physiological effects of orotic acid will be discussed. Since there are many studies devoted to orotic acid biosynthesis, incorporation, metabolic transformation, physiological and therapeutic roles, only about 500 references, which are believed to cover the main findings, will be presented. Data on the transformation and biological activity of orotic acid (summarized here) can be found elsewhere [20,21,64–69].

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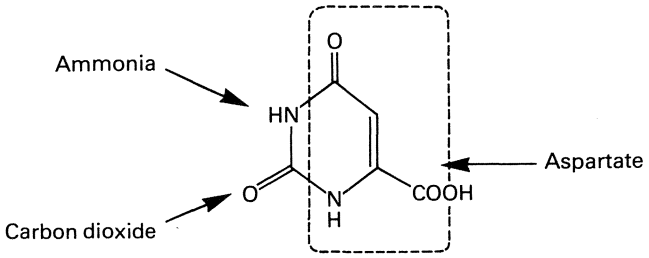
2. Pathway of Pyrimidine Synthesis de Novo

Higher organisms and many micro-organisms do not require exogenous pyrimidines and can synthesize pyrimidine nucleotides from simple precursors. In 1944 it became apparent that orotic acid is involved in the synthesis of pyrimidines *de novo* and a few years later it was evident that it is a precursor of nucleic acids [70,71].

The small-molecule precursors of orotic acid were identified by Reichard and Lagerkvist [72]. During *in vitro* incubation, liver slices incorporated labelled ammonia, bicarbonate and aspartate into pyrimidine components of RNA. When the slices were incubated with the labelled precursors in the presence of extracellular orotate, isotopes were found in this extracellular fraction. In this way, orotic acid was recognized as an intermediate in pyrimidine synthesis *de novo*. The labelled orotate was chemically degraded and small molecules identified as the precursors of particular atoms of the orotate ring, as shown in the following scheme:



Nutrition studies in bacteria indicated that carbamoyl aspartate (also known as ureidosuccinate) is an intermediate in pyrimidine biosynthesis. Finally, uridine nucleotides were found as end products of pyrimidine synthesis *de novo* [73]. The sequence of reactions leading to the synthesis of UMP is designated as the orotate pathway or pyrimidine synthesis *de novo* in distinction to the salvage pathway.

The salvage pathway utilizes preformed pyrimidines and purines for the synthesis of nucleic acids and is highly active in various types of cells. Uridine kinase plays a key role in the pyrimidine salvage pathway and its concentration is considered to reflect the relative efficiency of the system in utilizing preformed pyrimidines [74]. Adenosine kinase plays a similar role in making use of preformed purines [75]. It should be noted, however, that uridine and adenosine kinases are not the only enzymes involved in the salvage pathway and other deoxynucleoside kinases, phosphorylases, and phosphoribosyltransferases [76] also have important roles.

As already mentioned, carbamoyl aspartate was recognized as an intermediate in the synthesis of orotic acid [77]. In ureotelic livers, it is

synthesized from ammonia, carbon dioxide and aspartic acid in a two-step process, involving the formation of carbamoyl phosphate. When using a rat liver enzyme preparation, ATP and glutamate are necessary for its synthesis. Carbamoyl phosphate is required for the synthesis of urea and arginine, in addition to the synthesis of pyrimidines.

Carbamoyl phosphate synthesis from ammonia represents one of the prominent activities in ureotelic livers [78]. The enzyme requires *N*-acetylglutamate and is distinct from the enzyme responsible for carbamoyl phosphate synthesis in extrahepatic tissues and in the livers of uricotelic animals. This second enzyme utilizes glutamine [79], rather than ammonia as the primary nitrogen donor and is found in mushrooms, *Escherichia coli*, yeast, Ehrlich ascites tumour and several other animal tissues [80]. This enzyme is carbamoyl phosphate synthetase II (ATP: carbamate phosphotransferase, EC 2.7.2.2) and catalyses the following reaction:

$$\underset{\text{(or ammonia)}}{\text{Glutamine} + HCO_3^- + 2\text{ATP}} \xrightarrow{K^+,\ Mg^{2+}} \text{glutamate} + \text{carbamoyl phosphate} + 2\text{ADP} + P_i$$

It differs from the Type I enzyme [81] in that both glutamine and ammonia are substrates, although in animal cells glutamine is probably the physiological substrate. A highly active mitochondrial carbamoyl phosphate synthetase I is essential for the detoxication of ammonia through the urea cycle in mammalian livers.

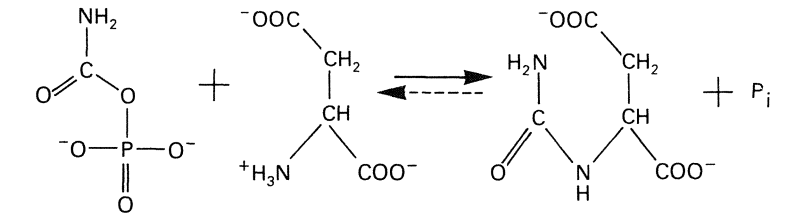
Glutamine-dependent carbamoyl phosphate synthetase II [82,83] is sensitive to allosteric inhibition by UTP and to allosteric activation by 5-phosphoribosyl-1-pyrophosphate (PRPP). Ammonia- and *N*-acetylglutamate-dependent carbamoyl phosphate synthetase I is neither activated by PRPP nor inhibited by UTP. The sensitivity of the Type II enzyme to feedback inhibition by UTP supports its role in the control of pyrimidine synthesis *de novo*. The enzyme is widely distributed in animal tissues as well as in lower organisms, providing carbamoyl phosphate for pyrimidine biosynthesis [84,85]. The activity of glutamine-dependent synthetase in the tissues is relatively low so it can limit pyrimidine synthesis. Pyrimidine synthesis in the liver *in vivo* is subject to feedback control as can be demonstrated by the immediate stimulation of UMP synthesis by depletion of the end product [86]. A valuable tool in studies of UMP synthesis *de novo* is the depletion of hepatic UTP by D-galactosamine. Using isolated perfused rat livers the concentration of UTP can be reduced in the intact organ to below the normal physiological level [86]. Under these conditions the incorporation of bicarbonate is highly stimulated, providing evidence that glutamine-dependent carbamoyl phosphatase is the site of feedback regulation of liver pyrimidine nucleotide synthesis *in vivo* [87]. Furthermore, the measurement of the rate of incorporation of labelled precursors into orotic acid in slices of various rat tissues demonstrated the operation of a feedback control mechanism

governing the rate of pyrimidine synthesis in intact cells and provided evidence that the reaction catalysed by carbamoyl phosphate synthetase II is the site of end product inhibition [88].

Recently a regulatory link has been established between the pathways of pyrimidine and arginine biosynthesis, each of which utilizes carbamoyl phosphate [89]. Orotate exercises an allosteric effect on ornithine transcarbamylase and this effect is dependent upon both the carbamoyl phosphate and ornithine concentrations. When the carbamoyl phosphate level is high, orotate has the effect of changing the normally negative co-operativity of ornithine transcarbamylase to a positive one, thus accelerating the conversion of carbamoyl phosphate in the arginine biosynthetic pathway.

When the carbamoyl phosphate level is low, however, orotate only activates the enzyme at low ornithine concentrations and actually causes inhibition when there is a lot of ornithine available. These interactions seem to be designed to achieve the best use of the carbamoyl phosphate, and to ensure that a certain amount is always available for the pyrimidine synthesis pathway. Regulatory interactions between different metabolic pathways are termed as metabolic interlock [90].

During pyrimidine synthesis, carbamoyl phosphate is utilized in a reversible reaction with the equilibrium shifted in favour of the synthesis of carbamoyl aspartate. The reaction is catalysed by aspartate carbamoyltransferase (carbamoyl phosphate: L-aspartate carbamoyltransferase, EC 2.1.3.2) which is widely distributed in nature. Rapidly growing tissues including various tumours are endowed with high levels of this enzyme [91].



Carbamoyl phosphate Aspartate Carbamoyl aspartate

Bacterial aspartate carbamoyltransferase is subject to allosteric inhibition [92] by CTP, one of the end products of the pathway. The enzyme from *E. coli* has been extensively studied because of its regulatory properties [92–94]. The native molecule consists of three regulatory subunits and two catalytic ones. However, three different classes of aspartate carbamoyltransferase have been recognized in different bacterial species, differing in molecular size and kinetic properties [95]. The enzyme has also been demonstrated in a number of animal tissues [96] and together with carbamoyl phosphate synthetase II and dihydro-orotase was found in

the soluble fraction of cells (in contrast to carbamoyl phosphate synthetase I [78] which takes part in the synthesis of urea and is located in mitochondria).

Although aspartate carbamoyltransferase appears to be a control site in the synthesis of pyrimidines in *E. coli* (and probably other micro-organisms) the corresponding transferase in animal cells does not appear to be a regulatory enzyme. Furthermore, since its activity in various tissues is far greater than that of carbamoyl phosphate synthetase II, animal aspartate carbamoyltransferase is not the rate-limiting enzyme in the pathway.

The conversion of carbamoyl aspartate to orotic acid became evident in work by Lieberman and Kornberg [97] who studied the degradation of orotic acid by an orotate-fermenting bacterium, *Zymobacterium oroticum*, and isolated two intermediates, dihydro-orotate and carbamoyl aspartate. The degradation reactions were found to be reversible and the cell-free extract of *Z. oroticum* converted carbamoyl aspartate back to orotic acid.

The enzyme catalysing the reversible cyclization of carbamoyl aspartate to dihydro-orotate is called dihydro-orotase (L-4,5-dihydro-orotate amino-hydrolase, EC 3.5.2.3). Dihydro-orotase was found in various animal tissues and for the catalytic function requires Zn^{2+} ions [98]. Orotic acid was found to be a competitive inhibitor of dihydro-orotate synthesis though a variety of other pyrimidines had no effect on enzyme activity [99].

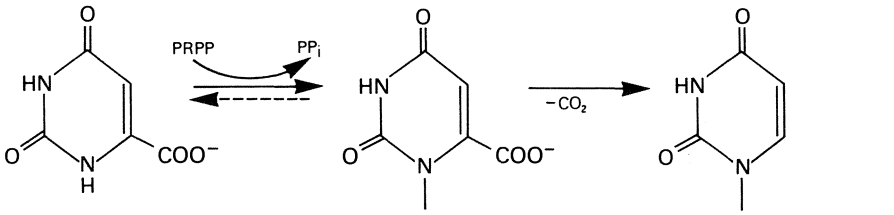
The second reaction is catalysed by dihydro-orotate dehydrogenase (L-4,5-dihydro-orotate: oxygen oxidoreductase, EC 1.3.3.1). The enzyme reversibly catalyses the reduction of orotate by NADH and aerobic oxidation of both NADH and dihydro-orotate [100]. Dihydro-orotate dehydrogenase from *Z. oroticum* is a flavoprotein [101] containing FMN, FAD and non-haem iron in a molar ratio 1:1:2. The ferrocyanide–ferricyanide oxidation–reduction couple was found to substitute for oxygen as an intermediate electron carrier in the reduction of cytochrome *c*. Oxygen, therefore, is not an obligatory mediator of the reaction catalysed by dihydro-orotate dehydrogenase [102].

Dihydro-orotate-oxidizing activity in rat liver homogenates can be recovered completely in the mitochondrial fraction [103,104]. With the exception of this system all the other enzymes of the orotate pathway appear to be present in the soluble cytosolic fraction. Dihydro-orotate dehydrogenase from rat liver was found to be located on the outer surface of the inner membrane of mitochondria [105]. Dihydro-orotate can diffuse freely from the cytosol into the mitochondria and orotate can diffuse freely from the mitochondria into the cytosol. Therefore no active transport of either dihydro-orotate or orotate is required in pyrimidine synthesis [105]. In addition to inhibiting dihydro-orotase, orotic acid strongly blocks [103] dihydro-orotate oxidation.

However, the activities of enzymes involved in the liver in the early stages of pyrimidine synthesis were found to increase following the administration of a diet supplemented with 1% orotic acid [106]. This has

been demonstrated for both aspartate carbamoyltransferase and dihydro-orotase.

The elucidation of the last steps of pyrimidine synthesis *de novo* came from the study of Hurlbert and Potter [107] which showed that uridine nucleotides were intermediates in the conversion of orotate to pyrimidines of nucleic acids. UMP was the first of the three uridine 5′-phosphates to become labelled in this process [108]. The synthesis of UMP from orotate takes place in two steps: the stoichiometric condensation [109] of orotic acid with 5-phosphoribosyl-1-pyrophosphate (PRPP) to form orotidine 5′-phosphate and its subsequent irreversible decarboxylation to UMP:



Orotate Orotidine 5′-phosphate Uridine 5′-phosphate

The first reaction is catalysed by orotate phosphoribosyltransferase (orotidine 5′-phosphate: pyrophosphate phosphoribosyltransferase, EC 2.4.2.10) which is readily reversible. The equilibrium constant for the forward reaction [109] is about 0.1. The reaction is specific for orotate (the enzyme usually does not accept uracil) and some synthetic analogues of orotic acid (Chapter 6). Orotate phosphoribosyltransferase activity was found in many animal tissues [110] and there are several phosphoribosyl-transferases of broad specifity which are distinct from the enzyme involved in the orotate pathway [111–113].

Orotidylic acid decarboxylase (orotidine 5′-phosphate carboxy-lyase, EC 4.1.1.23) catalyses the only irreversible step in the pyrimidine synthesis *de novo*. The enzyme is competitively inhibited by UMP and CMP [114–116] and some anomalous pyrimidine nucleoside 5′-monophosphates. The activity of orotidylic acid decarboxylase in excess of that of orotate phosphoribosyltransferase accounts for the absence of orotidine 5′-phosphate in the pool of low molecular weight compounds in animal cells.

The cytidine 5′-phosphates do not have an independent pathway of *de novo* synthesis and are derived from uridine 5-phosphates by an amination which occurs at the level of 5′-triphosphates:

$$\text{OMP} \rightarrow \text{UMP} \rightleftarrows \text{UDP} \rightleftarrows \text{UTP} \rightarrow \text{CTP} \rightleftarrows \text{CDP} \rightleftarrows \text{CMP}$$

The reaction requires [117] glutamine, Mg^{2+} ions, and non-stoichiometric amounts of GTP acting as an allosteric effector:

$$\text{UTP} + \text{ATP} + \text{glutamine} \xrightarrow{\text{GTP, } Mg^{2+}} \text{CTP} + \text{ADP} + \text{glutamate} + P_i$$

There is no evidence for the enzyme deamination of cytidine 5′-phosphates, although deoxycytidylate deaminase is a well known enzyme [118,119]. The direct conversion of cytidine compounds to uridine ones occurs by the deamination of cytidine or cytosine.

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3. Aggregation of Enzymes of the Orotate Pathway

During purification and heat denaturation experiments the activity of orotidylic acid decarboxylase appears to parallel orotate phosphoribosyltransferase activity. Also under a variety of physiological conditions both enzymes show closely parallel, co-ordinate changes in activity [120–122]. Orotate phosphoribosyltransferase from murine leukaemia P 1534 J (utilizing as the substrate orotate and 5-fluorouracil) was found to exist as a complex with orotidylic acid decarboxylase (123). Both enzyme activities were eluted together during gel filtration, co-sedimented in sucrose gradients, and remainded associated during salt fractionation. However, they could be separated into a phosphoribosyltransferase and decarboxylase component when enzyme preparations previously subjected to limited proteolysis by elastase were sedimented in sucrose gradients [123].

A gene affecting orotate phosphoribosyltransferase and orotidylic acid decarboxylase does not affect a third, metabolically adjacent enzyme, dihydro-orotate dehydrogenase [124]. Both erythrocytes and cultured diploid cell strains from patients with orotic aciduria (Chapter 5) are deficient in orotate phosphoribosyltransferase and/or orotidylic acid decarboxylase [125]. When mutant homozygous cultures are grown in a medium containing inhibitors of the orotate pathway (5-azaorotate or 6-azauridine), the cells develop nearly normal activity of both enzymes [125,126]. The effect is demonstrable even when the medium contains the product of the pathway (uridine or cytidine) in sufficient amounts to overcome the nutritional requirement imposed on the cells by the inhibitors. However, both drugs do not increase the activity of dihydro-orotate dehydrogenase [124,126]. The pyrimidine pathway is thus subdivided into groups of concurrently responding enzymes.

There are several studies on the effect of allopurinol and its metabolic derivatives on orotate phosphoribosyltransferase and orotidylic acid decarboxylase [127–129]. The administration of allopurinol to rats results in an increased urinary excretion of orotic acid and orotidine [127,130,131], and in elevated activities of orotate phosphoribosyltransferase and orotidylic acid decarboxylase in erythrocytes [128,129]. Also, in man, the administration of allopurinol and oxipurinol leads to an increase in the specific activity of orotate phosphoribosyltransferase and orotidylic acid decarboxylase [129]. The enzymes were found to exist in a complex as three different molecular species with molecular weights of 55 000, 80 000 and 113 000 daltons. The larger forms of the complex were more stable than the smaller one. In the presence of allopurinol or oxipurinol ribonucleotides (but not the corresponding free bases) the largest, most stable species predominated [129].

Although allopurinol and oxipurinol are potent inhibitors of UMP synthesis [120,131] through the inhibition of orotidylic acid decarboxylase (oxipurinol with a 2,4-diketo pyrimidine ring is capable of acting as an analogue of orotic acid, and 1-ribosyl-oxipurinol 5′-phosphate [132] is a

very effective inhibitor of orotidylic acid decarboxylase) the administration of allopurinol and oxipurinol is followed by an increase of the specific activity of both orotate phosphoribosyltransferase and orotidylic acid decarboxylase [120,127,133]. This effect is attributed to the stabilization of the enzymes [134] or the enzyme complex, the metabolites of allopurinol shifting the complex to a larger and more stable form [129].

There are several reports by Jones and co-workers dealing with the purification, properties and conformation of the orotate phosphoribosyltransferase and orotidylic acid decarboxylase enzyme complex present in mouse Ehrlich ascites cells [135–137]. Multiple molecular forms of orotidylic acid decarboxylase from human erythrocytes and human liver were studied by O'Sullivan and co-workers [138,139]. A bifunctional enzyme complex of orotate phosphoribosyltransferase and orotidylic acid decarboxylase occurs also in mouse liver and brain [140], regardless of the developmental stage of the animal. Both enzyme activities remained co-ordinate in fetal, neonatal, immature and adult liver and brain.

A parallel co-purification similar to that involving the enzymes taking part in the final stages of UMP synthesis *de novo* is found in the case of aspartate carbamoyltransferase with carbamoyl phosphate synthetase in baker's yeast [141]. The two enzyme activities co-eluted from gel filtration on Sepharose 6B together with the feedback site and retained full sensitivity to feedback inhibition by UTP. Analytical ultracentrifugation revealed two major peaks and sucrose gradient centrifugation in the presence of UTP, glutamine and Mg^{2+} ions resulted in co-sedimentation of the two activities and the regulatory site, corresponding to a molecular weight of 800 000 daltons [141]. Omission of glutamine and Mg^{2+} ions from the sucrose gradient caused a distinct peak of carbamoyl phosphate synthetase to trail behind the aspartate carbamoyltransferase. This, together with genetic data [142] supports the view that the gene which controls both enzymes and a regulatory site at which UTP causes feedback inhibition of both activities is a polycistronic operon, coding for the production of two or three polypeptide chains which are associated in a multifunctional aggregate [141].

Five of the enzymes of UMP biosynthesis exist in the soluble fraction of Ehrlich ascites carcinoma as two enzyme complexes [143]. One complex contains the first three enzymes of the pathway, carbamoyl phosphate synthetase, aspartate carbamoyltransferase and dihydro-orotase and has an apparent molecular weight of 800 000 to 850 000 daltons. The second enzyme complex contains orotate phosphoribosyltransferase and orotidylic acid decarboxylase and sediments in a sucrose gradient with 30% dimethyl sulphoxide and 5% glycerol with an apparent molecular weight of 105 000 to 115 000 daltons [143].

Glutamine-dependent carbamoyl phosphate synthetase, aspartate carbamoyltransferase and dihydro-orotase were co-purified as a high molecular weight complex from an extract of unfertilized eggs of *Rana catesbeiana* [144]. UTP was required to maintain the integrity of the complex during

the last purification steps and its removal resulted in the dissociation of the complex. Incubation of a mixture of the dissociated enzymes with UTP and Mg^{2+} ions led to their reassociation into the high molecular weight complex.

Similar complexes were observed in rat livers and in other tissues [145–149]. The extensively purified complex of glutamine-dependent carbamoyl phosphate synthetase, aspartate carbamoyltransferase and dihydro-orotase from rat liver had a sedimentation coefficient of 27 S (approximately 900 000 daltons). Treatment of the complex with pancreatic elastase caused a selective inactivation of carbamoyltransferase with concomitant dissociation of the complex [159].

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4. Efficiency and Regulation of Pyrimidine Synthesis

There are only a few studies dealing with the cellular uptake of orotic acid. The incorporation of orotic acid into whole cells can be stimulated more than 90-fold by a combination of PRPP and a heat labile factor [150], probably orotate phosphoribosyltransferase. It is assumed [151] that the enzyme attaches to the cell membrane and in the presence of external orotic acid and PRPP leads to the formation of internal orotidine 5'-phosphate. In bacteria the orotate is taken up similarly [151] by a process of group translocation across the membrane involving the participation of orotate phosphoribosyltransferase and requiring PRPP.

On the other hand, there are many reports dealing with the control of pyrimidine biosynthesis [152–154] and especially with the incorporation of orotic acid into RNA and DNA in various biological systems and different experimental conditions [155–176]. The labelled orotic acid was utilized as a useful tool to solve a number of biochemical, pharmacological, physiological, and nutritional problems [177–185]. The degradation of orotic acid is accomplished by a set of reactions which are the reverse of those taking place during the synthesis of orotic acid from low molecular weight precursors. The decarboxylation of orotic acid in some strains of *Mycobacterium*, resulting in the direct formation of uracil was also proposed [186] but this finding awaits further confirmation.

Since the sequence of reactions in the orotate pathway was established mainly in studies with adult rat livers, there are continuing attempts to demonstrate a similar sequence of reactions in other biological systems. For example, the enzymes of the orotate pathway are not very active in fetal rat livers [187]. Orotic acid injected into pregnant females is incorporated to a lesser extent into fetal hepatic RNA than into hepatic RNA of adult rats although the placenta does not block the uptake of orotic acid. However, there is a considerable incorporation of orotic acid on the second day after birth [187] and the specific activity of the weanling rat hepatic RNA attains a superior value to that found in the adult rats. There are several reports dealing with the role of the orotate pathway during development [188–191].

For a long time it has not been known whether the brain itself supplies pyrimidine precursors for the synthesis of RNA *de novo* or whether these precursors must be supplied preformed from extraneural sources. Evidence has been obtained [192] that neural tissue has little capacity for synthesizing pyrimidine nucleotides for its own metabolic needs *de novo*. The incorporation studies in rats suggest that the brain utilizes preformed pyrimidines to a much greater extent than it utilizes the *de novo* pathway. This underlines the importance of the liver and other peripheral organs in the maintenance of normal RNA metabolism of the brain [192], although the brain contains the enzymes of pyrimidine synthesis *de novo* [193,194].

Measurements of the incorporation of labelled bicarbonate into orotic acid established the occurrence of the complete pathway of *de novo*

pyrimidine synthesis in rat brain [191]. However, the activity of the orotate pathway is very high in fetal brain and declines rapidly with neural development. The mature rat brain exhibits less than 1% of the activity of the fetal brain at 18 days of gestation. It was supposed that the variation in the ability of the brain to synthesize orotic acid *de novo* is determined by a similar variation in its ability to synthesize carbamoyl phosphate [191].

In avian species a similar question has been investigated, namely, whether the ability to synthesize pyrimidines *de novo* is confined to the liver which may serve as a source of pyrimidines to the extrahepatic tissues, or whether the orotate pathway is active in extrahepatic tissues as well. The data obtained using estrogen-stimulated chick oviduct indicate that extrahepatic tissues of avian species meet their requirements for pyrimidine nucleotides through *de novo* synthesis rather than depending upon the liver or other exogenous sources for a supply of formed pyrimidines [195]. The observation that the rate of pyrimidine synthesis is sensitive to inhibition by purines suggests that the regulation of the biosynthesis of purine and pyrimidine nucleotides might be linked through a common metabolic effect. The data indicate that the reaction catalysed by carbamoyl phosphate synthetase II is the site of this inhibition [195].

Several findings suggest that glutamine-dependent carbamoyl phosphate synthetase and orotate phosphoribosyltransferase are important in the control of UMP synthesis *de novo*. The enzymes have distinct peaks of activity during the S phase of the cell cycle of synchronized HTC cells while very little activity during the G_2 and M phase has been observed [196]. Whereas carbamoyl phosphate synthetase activity increases rapidly during early G_1, orotate phosphoribosyltransferase activity is enhanced only at the late G_1. The stimulated *de novo* pyrimidine synthesis during the S phase serves primarily as a source of nucleotides for RNA synthesis, which reaches a peak during this phase of the cell cycle. In addition, the peak in enzyme levels during the S phase of the cell cycle suggests that both enzymes have a short half-life, their formation is periodic, and the main synthesis takes place during the S phase [196].

Factors responsible for the control of pyrimidine nucleotide synthesis in intact cells have also been investigated using rat hepatoma cells growing in culture [197]. The addition of uridine to the culture medium caused a marked decrease in the rate of *de novo* pyrimidine synthesis. Uridine caused an inhibition of orotate phosphoribosyltransferase and did not affect the activity of carbamoyl phosphate synthetase II, aspartate carbamoyltransferase, dihydro-orotase or orotidylic acid decarboxylase. These findings suggest that in rat hepatoma cells in culture orotate phosphoribosyltransferase might be rate-limiting in the synthesis of UMP [197].

On the other hand, the pattern of an increase of orotate phosphoribosyltransferase activity in regenerating rat livers suggests that the enzyme is not rate-limiting for RNA synthesis at the early stages of liver regeneration [198,199], since the activities of enzymes of the orotate pathway either vary little at the early post-operative stages or increase significantly only many

hours after the major changes in RNA synthesis have taken place [200–202].

The results from different laboratories underline the importance of knowledge of the precursor uptake and pools for evaluation of biosynthetic processes [203–206]. Perfused regenerating livers produce 2.5 times as much UMP per gram of liver as do perfused normal livers [205]. However, the absolute amount of orotic acid converted into UMP is higher in perfused normal livers than in regenerating ones. It seems that the levels of total orotic acid uptake and UMP synthesis are similar in intact and regenerating livers of the same size and that the total amount of orotic acid taken up, and the size of the liver are what determine UMP production [205].

At 1 hour after partial hepatectomy there is a 60–100% increase in the capacity of the liver to concentrate [^{3}H]orotate with respect to the radioactivity in plasma [206]. The increase in intracellular radioactivity was already detectable 10 min after operation. The effect of partial hepatectomy on precursor entry was restricted to the liver and has been found to also alter the uptake of thymidine and uridine without any change in the metabolism of orotic acid [206].

A high rate of orotic acid uptake is a common feature of the liver and kidney. However, a transport mechanism for orotic acid is impaired in hepatic neoplasia [207]. Also the uptake of orotate by three transplanted kidney tumours was found to be less than 5% of that in the host kidney cortex [208]. An explanation of the decrease in orotate uptake by liver and kidney tumours is not yet known.

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5. Alterations in Orotic Acid Excretion

Enhanced excretion of orotic acid was observed under different physiological [209,210] and nutritional [211–217] conditions. The amount of orotic acid excreted during human pregnancy is about 20–40 mg per day and does not vary substantially during the course of pregnancy [209,210]. Inherited deficiencies of the urea cycle [218], purine nucleoside phosphorylase [219], and especially of orotate phosphoribosyltransferase and orotidylic acid decarboxylase also result in an increased excretion of orotic acid.

In children, deficient levels of ornithine carbamoyitransferase (an enzyme involved in the urea cycle, and which converts ornithine and carbamoyl phosphate to citrulline) [218,220] present as orotic aciduria, a secondary effect resulting indirectly from the accumulation of carbamoyl phosphate. The deficiency of ornithine carbamoyltransferase leads to overall stimulation of pyrimidine synthesis *de novo* which is reflected by an increased production and excretion of orotic acid.

'Classical' orotic aciduria is a rare autosomal recessive disorder which is characterized by retarded growth and excretion of large quantities of orotic acid in the urine [221,222]. The disease was described in 1959 as an inborn error of pyrimidine biosynthesis in patients with crystals of orotic acid in the urine [223]. The urinary excretion of orotic acid by these patients was 1.34 g per day in contrast to approximately 0.014 g per day excreted by normal individuals [222,224]. When the diet of patients was supplemented with uridine, clinical remission and a remarkable reduction in orotic acid excretion took place [221,225,226].

A disorder of pyrimidine excretion somewhat comparable to congenital orotic aciduria [227–229] may be produced (Chapter 6) by the administration of several drugs affecting pyrimidine synthesis *de novo* [230–238].

Orotic aciduria is due to homozygosity for a Mendelian gene affecting the activity of two final enzymes of pyrimidine synthesis *de novo* [239,240]. Individuals homozygous for the mutation are biochemically characterized [210,240] by one of two phenotypes. Type I is most prevalent and exhibits deficient or decreased activity of orotate phosphoribosyltransferase and orotidylic acid decarboxylase while type II is characterized by a deficiency of only the decarboxylase. It was proposed that the deficiency of the two sequential enzyme activities in orotic aciduria is consistent with a defect in a genetic control mechanism [241]. Evidence discovered by Worthy and Kelley [242] suggested, however, that the molecular defect is due to a mutation in a gene that affects the structure of either orotidylic acid decarboxylase or orotate phosphoribosyltransferase and cannot be attributed to a mutation in a regulatory gene.

Orotidylic acid decarboxylase from homozygous mutant cells was found to be more thermostabile and exhibited different electrophoretic mobility when compared to the enzyme from normal cells [243]. Although the differences have been shown for this enzyme only, they could reflect alterations in the primary structure of either orotidylic acid decarboxylase

or orotate phosphoribosyltransferase since they exist in a complex. Moreover, orotidylic acid decarboxylase itself may be composed of subunits which are in dynamic equilibrium with the aggregate form [244].

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6. Inhibitors of the Orotate Pathway

The first known drug affecting the orotate pathway was 6-azauridine [245,246]. This analogue is phosphorylated to 6-azauridine 5′-monophosphate which acts as a competitive inhibitor of orotidylic acid decarboxylase [247]. Therapeutic use of 6-azauridine [248,249] is occasionally complicated by a pronounced crystalluria. Owing to the block of orotidylic acid decarboxylase, large amounts of orotidine and orotic acid are excreted in urine. After the infusion of 6-azauridine the excretion of orotic acid precedes orotidine and the former disappears more rapidly from the urine. Psoriatic patients on azaribine (triacetylated form of 6-azauridine given orally) excreted 0.2–1.3 g of orotic acid and orotidine per day [250].

The reduction in urinary excretion of both compounds following uridine therapy reflects the utilization of uridine for the formation of UMP by the salvage pathway. A similar phenomenon was observed in hereditary orotic aciduria following uridine replacement therapy which bypasses the congenital enzyme defect (Chapter 5). The reversal of 6-azauridine-induced orotic aciduria by hydroxyurea, methotrexate and cyclophosphamide [251] (i.e. by the drugs affecting the synthesis of DNA without any effect on orotic acid synthesis) suggests that the control of pyrimidine synthesis *de novo* is linked to DNA synthesis.

Murine lymphoma cells in culture exposed to 6-azauridine also accumulate orotic acid and orotidine, but no detectable amount of orotidine 5′-phosphate [252]. In homogenates of the cells the presence of a membrane-bound phosphatase with activity for orotidine 5′-phosphate was demonstrated. When incubated with homogenate the nucleotide was converted to orotidine in the absence of inorganic phosphate, but it was converted to orotic acid in the presence of phosphate, suggesting the presence of orotidine phosphorylase [252].

An inhibitory effect on orotidylic acid decarboxylase was also observed following 5-azacytidine [253,254], another highly active cytostatic agent [253–256]. The direct action of 5-azacytidine 5′-phosphate on enzyme activity *in vitro* has not yet been measured and the evidence for its interaction with the transformation of orotic acid came from the observation that 5-azacytidine increases its urinary excretion in mice [257,258]. The activity of orotidylic acid decarboxylase in liver extracts from 5-azacytidine-treated animals was also decreased in comparison to controls [258].

However, 5-azacytidine displays a dual effect on the uptake of orotic acid into liver RNA. Whereas the short-term treatment resulted in a block of RNA synthesis, the incorporation of orotic acid was extensively increased when 5-azacytidine had been given at longer time intervals before orotic acid [258,259]. A four-fold increase in the uptake of orotic acid into RNA was observed 18–24 hours after 5-azacytidine, without any preferential labelling of individual types of liver RNA. However, since in

fasting animals the uptake of orotic acid into liver RNA was enhanced equally and no additional stimulatory effect of 5-azacytidine was observed, it was suggested that the enhanced uptake of orotate into liver RNA reflects the action of the drug on the gastrointestinal tract. This was later confirmed by measuring the effect of 5-azacytidine on gastric secretion [260]. Cycloheximide too, despite having no effect on orotic acid metabolism, enhances the incorporation of orotate into liver RNA [261] and simultaneously depresses gastric secretion [262].

There are several synthetic derivatives of orotic acid and pyrimidine analogues which, after their conversion, interfere with the activity of orotidylic acid decarboxylase [263,264]. While 6-azacytidine 5′-phosphate is only one tenth as active as 6-azauridine 5′-phosphate [265], 5-hydroxyuridine 5′-phosphate [266] and aminouridine 5′-phosphate [267] are potent inhibitors of orotidylic acid decarboxylase. The inhibitory action of allopurinol and of its metabolites on pyrimidine synthesis *de novo* [268] was mentioned in Chapter 3.

5-Fluoro-orotic acid undergoes in the liver the same conversion as orotic acid [269,270]. The 5-fluoro analogue serves as a substrate for orotate phosphoribosyltransferase [270] and the anomalous nucleoside 5′-phosphate so produced inhibits orotidylic acid decarboxylase. A number of 5-substituted orotic acid (5-chloro, 5-bromo, 5-amino, 5-nitro and 5-methyl) analogues were found to be inactive when examined for their ability to react with or inhibit orotate phosphoribosyltransferase [270].

However, 5-fluoro-orotic and orotic acids are utilized differentially for the synthesis of cytoplasmic liver RNA. 5-Fluoro-orotate is incorporated preferentially into a fraction of non-ribosomal RNA which has several properties in common with messenger RNA [271]. Analysis of microsomal RNA showed little or no incorporation of 5-fluoro-orotic acid into either 18 S or 28 S ribosomal RNA. The analogue is rapidly incorporated into 45 S ribosomal precursor RNA but its subsequent processing into mature 18 S and 28 S RNA is inhibited [272]. The analogue also greatly inhibits the incorporation of orotic acid into ribosomal RNA but has little effect on its incorporation into messenger RNA [273].

5-Azaorotic (oxonic) acid represents another analogue of orotic acid with cytostatic activity [274]. The drug inhibits metabolic transformation and incorporation of orotic acid in the liver and kidney [275]. Similarly to 6-azauridine, 5-azacytidine and allopurinol, the administration of 5-azaorotate results in an increased urinary excretion of orotic acid and orotidine [276]. 5-Azaorotate markedly depresses the activity of orotate phosphoribosyltransferase [275,277]. However, an increased level of orotidine 5′-phosphate in the liver of drug-treated animals indicated a polyvalent inhibitory mechanism [278].

By analogy with 5-fluoro-orotate, [270] 5-azaorotate was found to react with PRPP blocking simultaneously and in a competitive manner the phosphoribosyltransferase reaction. The newly formed 5-azaorotate 5′-phosphate and/or 5-azauridine 5′-phosphate then inhibit orotidylic acid

decarboxylase [276,278]. The biological effect of 5-azaorotate depends on its metabolic conversion which is different in different target tissues [279,280]. In bacterial systems and L5178Y leukaemia cells the drug is less effective than in the liver or kidney [275]. Dihydro-5-azaorotic acid specifically inhibits dihydro-orotate dehydrogenase [281].

Barbiturates represent another group of inhibitors of the orotate pathway [282,283]. These pyrimidine derivatives affect dihydro-orotate dehydrogenase [284,285]. It was supposed that barbiturates interfere with dehydrogenase activity by binding to flavine coenzymes resulting in the formation of an inactive complex [285]. Amobarbital has been shown to inhibit the incorporation of orotic acid into RNA in exponentially growing cells of *Bacillus cereus* [286] without having any effect on its metabolic conversion. It was found that the drug markedly depressed the uptake of orotate into bacterial cells [286].

A series of other barbiturates (phenobarbital, barbital, thiopental, pentobarbital at 1 mmol l^{-1} concentration inhibit the orotate uptake system without affecting the incorporation of uracil into cellular pyrimidines [287]. While barbituric acid and hexobarbital are less active, phenylethylhydantoin, chlorpromazine and phenethyl alcohol are extremely active. Phenobarbital also depresses the utilization of orotic acid for the synthesis of cytidine nucleotides in the liver [288]. α-Hexachlorocyclohexane, an inhibitor of the phenobarbital type, was even more effective in depressing *de novo* cytidine nucleotide synthesis from orotic acid [289].

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7. Induction of Fatty Liver in Rats

The administration of a purified diet supplemented with 1% orotic acid induces in rats a rapid accumulation of lipids in the liver [290]. Such an effect is species specific and does not seem to occur in humans. The deposition of triglycerides in the liver, accompanied by a decrease in the concentration of plasma lipids, is a common and characteristic feature of fatty liver induced by various drugs. The earliest biochemical change [291,292] detected in rats given orotic acid is an increase in the pool of uridine nucleotides paralleled by a concomitant reduction of the level of adenine nucleotides and the oxidized and reduced forms of NAD.

The fatty infiltration of the liver which accompanies the ingestion of orotic acid does not seem to be accompanied by serious pathological disturbances [293] and is readily reversible, unlike the development of fatty liver induced by a choline deficient diet. Supplementation of the orotic acid diet with adenine essentially modifies the effect of orotic acid [294]. Since PRPP is required for both the synthesis of purines and the metabolism of orotic acid, the decrease in the pool of adenine nucleotides is caused [295,296] by an inhibition of purine synthesis *de novo* due to extensive depletion of PRPP during the conversion of orotic acid to UMP. After the disappearance of orotic acid from the liver of animals previously fed a diet containing orotic acid, stimulation of the synthesis of adenine nucleotides occurred.

Fatty liver developed in rats fed a diet containing orotic acid is characterized by the deposition of droplets of triglycerides in the tubules of the endoplasmic reticulum [297,298]. The reticulum breaks down into individual vesicles which contain lipid droplets 0.2–0.5 μm in diameter which accumulate the apolipoproteins of low and very low density lipoproteins. The liver otherwise appears to be functionally normal, unlike that of animals receiving other lipotrophic agents. The administration of orotic acid has a specific effect on lipoprotein synthesis without overall inhibition of protein synthesis. The effect is selective for hepatic but not intestinal β-lipoprotein production and triglyceride transport [299].

Plasma β-lipoprotein concentration in rats receiving orotic acid falls to less than 1% of normal and rebounds to normal level within 48 hours following withdrawal of orotic acid [300]. When perfused *in situ*, the livers from orotic acid fed rats released α-lipoprotein, albumin, and other plasma proteins but no detectable β-lipoprotein. They also released smaller amounts of cholesterol and phospholipids than normal livers and no triglycerides, although they contained ten times the normal amount of triglycerides [300]. Since β-lipoprotein has a specific role in the normal transport of triglycerides, the fatty liver produced by orotic acid appears to result from the inhibition of synthesis or release of hepatic β-lipoprotein.

Plasma contains an apoprotein which combines with lipids in the liver to form plasma lipoproteins [301]. Rats treated with orotic acid did produce this apoprotein but the formation of plasma lipoproteins from apoprotein

is inhibited [302]. Orotic acid thus specifically depresses the formation of the very low density lipoprotein fraction without affecting the synthesis of the protein portion of the lipoprotein. The fat accumulated in the liver is newly synthesized and does not represent fat mobilized from other tissues.

While in rats following the administration of orotic acid the level of acid-soluble purines decreases, it is unaltered in chicks [303]. There is also no apparent increase in lipid concentrations in the liver of chicks after feeding of orotic acid [303,304]. The induction of fatty liver by orotic acid is highly specific; rat is a susceptible animal, but not the chick, mouse or monkey [305].

Concomitant with triglyceride accumulation in the liver of rats receiving orotic acid the liver peroxide content (lipoperoxides and lipohydroperoxides) is increased several times [306]. The alterations in hepatic lipid and nucleotide levels are prevented as well as reversed when an orotic acid-containing diet is supplemented with 0.25% adenine sulphate [294,307], 4-amino-5-imidazolecarboxamide [308] or allopurinol (as little as 0.05% in the diet [309] completely prevents the accumulation of fat in the liver). Beside these compounds several hypolipidaemic drugs are active in preventing triglyceride deposition in association with an increased level of the serum β-lipoprotein [310]. There is a number of reports dealing with the induction and prevention of the orotic acid fatty liver in rats [311–338].

The basic mechanism underlying the pathogenesis of fatty liver is a block in the release of triglycerides into the plasma [300,339]. Since triglycerides are released from the liver into the plasma in the form of lipoproteins the primary defect in fatty liver is either the synthesis or the secretion of lipoproteins, or both.

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8. Physiological Effects

Increasing experimental evidence indicates an important role of orotic acid in various cellular processes taking place in different types of cells and organisms. Orotic acid has been shown to stimulate the phagocytic activity of leukocytes [340–342] and of the reticuloendothelial system [343] by a process which can be abolished by pretreatment with hydrocortisone. Vitamin B_{12} and folic acid were found to strengthen the normalizing action of orotic acid on the haemopoiesis of animals subjected to a long-term exposure to toxic substances in low dose [344,345]. Orotic acid at a dose of 100 mg/kg body weight suppressed in rats the inhibitory action of thiophosphamide on blood formation [346].

Orotic acid stimulates the healing process. In mice with an experimental injury the daily oral administration of potassium orotate fastened the healing process, the differentiation of fibroblasts, and the formation and transfer of RNA from nucleus to cytoplasm [347]. Also the rate of collagen synthesis was higher during the stimulation of the wound healing process by potassium orotate [348].

The inhibitory effect of orotic acid (and of bovine milk containing orotate) on cholesterol synthesis was observed [349,350]. Orally administered orotic acid decreases the cholesterol level in whole serum and in serum β-lipoproteins, but increases its level in the liver of treated rats [351]. However, orotic acid did not affect the amount of glycolipids and cholesterol in the brain of lysine-deficient rats [352].

In the Soviet Union [353–357], Hungary [358–363], and especially in the German Democratic Republic the action of orotic acid on the central nervous system was studied. Orotic acid was found to affect the nerve cells during regeneration and also the size of the axon [364–366]. The combination of kavain with magnesium orotate prevents the appearance of disturbances in the function of the central nervous system characteristic of sustained hypoglycaemia [358]. There is a therapeutic consequence of this observation for gerontology since in the course of cerebrovascular ageing both the supply of glucose and its catabolism are below the requirements of the brain. Orotic acid was also found to affect functional disturbances in experimental lymphogenic encephalopathy [359] and to protect against neurotoxicity mediated by strychnine [360]. Orotate antagonized absolutely lethal doses of strychnine, with regard to both the prevention of convulsions and to the reduction of mortality.

Magnesium orotate glycinate complex exerts a protective effect on experimental ammonia poisoning [361,362]. In animals stressed neurotoxically by an insecticide carbamate derivative, the administration of magnesium orotate or orotic acid eliminated or lessened the negative reactions caused by the toxin [363]. Significant differences were also found with learning-dull rats, where orotic acid and its magnesium salt facilitated the learning process [367].

The physiological and pharmacological influence of orotic acid on the

teaching and memorization processes and the central nervous system generally, was studied by Matthies and co-workers [368–377] and by Rick and co-workers [378]. For the illustration only one finding will be presented. Orotic acid (100 mg/kg bodyweight per day), given intraperitoneally to rats for 14 days before or during elaboration of a conditional visual discrimination, delays the normal extinction of learned behaviour. The length for 50% extinction was 13 days in controls and 215 days in orotic acid treated animals [379].

This effect was inhibited by 6-azauridine [380] which blocks the conversion of orotate to UMP. However, since both UMP and CMP also improve memory extension even in the presence of 6-azauridine, the availability of pyrimidine nucleotides in the brain is likely to be a limiting factor for long-term memory. Orotate does not stimulate relearning directly but results probably in a higher supply of pyrimidine precursors for the increased brain RNA synthesis that occurs during the process (see also 381).

Orotic acid prevents experimental hepatitis induced by D-galactosamine. The experimental hepatitis paralleled by the accumulation of UDP derivatives of D-galactosamine was studied by Decker and co-workers [382–384]. On the basis of ultrastructural and biochemical analyses it was concluded that the liver damage observed after D-galactosamine treatment differs from that seen in human hepatitis in that the former leads to accumulation of liver triglycerides, hyperplasia of the smooth endoplasmic reticulum, and cell necrosis [385,386].

D-Galactosamine causes a trap mechanism which results in a marked decrease of the content of UTP, UDP, UMP, and UDP-sugars which are necessary for the normal synthesis of DNA and RNA in the liver. Pretreatment with orotic acid (and other pyrimidines) causes protection against the deficit of uridine 5′-phosphates, and no hepatitis-like liver damage is induced [387,388]. The galactosamine-induced hepatic injury was also studied following choline orotate [389,390], and later the protective role of orotic acid in drug-induced hepatitis in relation to the age of experimental animals was described [391,392]. The inhibitory action of various drugs on galactosamine-induced hepatitis can be found in the report by Pickering and co-workers [393].

Besides preventing experimental hepatitis, orotic acid displays a protective effect during liver tumorigenesis taking place in the presence of ethionine and some other carcinogens [394] and during carbon tetrachloride intoxication [395–399]. A single oral dose of 25 mg aicamine (4-aminoimidazole-5-carboxamide orotate) per kg administered to rats simultaneously with a subcutaneous injection of 1 ml carbon tetrachloride totally prevented its hepatotoxic effects [400]. Similarly, orotic acid at a dose of 50 mg/kg abolished the carbon tetrachloride-induced changes but failed to normalize the high hepatic content of lipids and triglycerides [400].

Orotic acid and lysine orotate decrease ethanol toxicity [401,402].

Ethanol inhibits (beside other processes) hepatic galactose elimination [403,404] probably owing to a block in UDP-glucose 4′ epimerase which is followed by the accumulation of UDP-galactose, trapping of UDP-glucose, and an increase of galactose 1-phosphate concentration [405]. Orotic acid decreases the effect of ethanol by increasing the level of UDP-glucose [405]. The action of orotic acid in relation to experimental galactosaemia and galactose cataract was also investigated [406–408].

The first studies dealing with the effect of orotic acid on the ultrastructure and enzyme level in the liver [409–415], bile secretion [416], liver regeneration [417], and liver glycogen synthesis [418–420] have been performed in the last 10–15 years. Recently, an abnormal metabolism of orotic acid associated with acute hyperammonaemia [421], renal gluconeogenesis in orotic acid fed rats [422], and the action of orotic acid on enchondral ossification [423] have also been studied.

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9. Orotic Acid in Human Therapy

Orotic acid is relatively insoluble compound but some of its salts and derivatives are more soluble and therapeutically highly active [424–432]. The clearance of orotic acid approaches that of creatinine [433], and during drug-induced orotic aciduria it exceeds glomerular filtration [434]. There is evidence that even high doses of orotic acid are not deleterious to human individuals except that they may occasionally obstruct urine flow by forming crystalline deposits [435].

Orotic acid is bound in the serum to proteins [436] and is metabolized in the liver [433]. The binding of orotic acid to serum proteins in children and adults receiving the drug orally at 80 mg/kg bodyweight per day for 28 days was less than 1% [437]. Maximal serum concentrations of orotic acid were attained 2–5 hours after intake and showed great individual variations, ranging from 0.8 to 10 μg per ml. On the other hand, the half-times for disappearance of orotic acid from the serum were about 1 hour and were more uniform [437]. The resorption of orotate was also followed in newborn infants [438], simultaneously with the level of enzyme activities in blood serum [439,440]. In connection with the anti-inflammatory effect of calcium orotate, [441] the calcium and phosphate metabolism in the treated patients was measured [442,443].

Orotic acid at high doses (3–6 g per day) was used with moderate success in adult patients with pernicious anaemia [444]. Kelley and co-workers [445] investigated the use of orotic acid in the treatment of hyperuricaemia. There was a 20–30% inhibition of purine biosynthesis and an increase in renal clearance of uric acid, but orotic acid offered no advantages over other available agents. Orotic acid in combination with vitamin B_{12} was used in children with disturbed memory [446], and in combination with Kanaform in patients with cerebral trauma and vascular affections [447].

In the Soviet Union orotic acid has been studied for a long time in relation to arteriosclerosis, myocardial infarction [449–450] and various cardiopathogenic changes [451–455]. The effect of precursors of nucleic acid synthesis on myocardial contractile function was followed by Zharov and others [456,457]. However, the effect of orotic acid on the development of myocardial hypertrophy was also studied in other countries [458–463].

Orotic acid has been used in the management of neonatal jaundice and of metabolic defects in icterus neonatarum [464–470]. A possible underlying mechanism contributing to the high levels of unconjugated bilirubin in the plasma of premature infants is a transient deficiency in the conjugating ability of the liver, catalyzed by UDP-glucuronyltransferase. Since a contributing factor could be a low level of UDP-glucuronate due to a low production of UMP, the administration of orotic acid and the resulting increase in the level of UMP and uridine coenzymes in the liver might stimulate the conjugation of bilirubin [471]. There appears to be no contraindication for the use of orotic acid for the treatment of hyperbili-

rubinaemia in premature infants. It is of interest that orotic acid does not have any effect on bilirubin levels in the mature newborn [466].

Kintzel and co-workers [465] achieved lowered levels of bilirubin using 300 mg orotic acid per day. The premature infants subjected to therapy had from the 3rd to the 6th day consistently 25–30% of the earlier serum bilirubin levels. A number of studies related to the effect of orotic acid on bilirubin level in premature infants was carried out under different conditions [472–480]. Recently, the combination of orotic acid with phenobarbital and adenine was tested [481] as a prophylactic preparation against premature hyperbilirubinaemia.

The major attention was devoted to the use of orotic acid, its inorganic salts and organic derivatives for the treatment of chronic and virus hepatitis [482–489] and other forms of liver insufficiency [490–492]. The beneficial effect of orotic acid and other pyrimidine (and purine) precursors of nucleic acids in the liver led to the appearance of several preparations containing orotic acid in combination with vitamins and other components which were used during the treatment of liver insufficiency. There is a number of clinical and experimental data obtained by Wildhirt [489, 496–498], Nieper [441–443], and others [499–506] which show the beneficial role of orotic acid during the treatment of various liver diseases and speak in favour of its therapeutic use.

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Uridine A8, B11, G1, H18, M23, R5, T6, T17

Vitamin A B1, D2

Vitamin B_{12} C2, C3, C4, C5, D9, D10, H15, H16, K52, M7, M9, M12, M47, P8, P9

Vitamin E B44, C19

Xanthine A1

Zinc N14